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Summary of AHRQ's Comparative Effectiveness Review of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

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Summary of AHRQ's Comparative Effectiveness Review of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease

C. Michael White, PharmD, FCP, FCCP, and Laurence Greene, PhD

Target Audience
Physicians, pharmacists, nurses, and case managers who manage patients with ischemic heart disease

Learning Objectives
Based on the findings from AHRQ's systematic review of research on angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) for treating stable ischemic heart disease (IHD) in patients with preserved left ventricular systolic function:

- Compare the effectiveness and safety of adding an ACE inhibitor or an ARB to standard therapy versus standard therapy alone
- Compare the benefits and harms of combined ACE inhibitor/ARB therapy plus standard therapy versus an ACE inhibitor or an ARB plus standard therapy
- Identify subpopulations of patients who might benefit from adding an ACE inhibitor, an ARB, or combination therapy to standard medical therapy
- Apply findings from the systematic review to guide decisions about patient-centered therapies for managing stable IHD and reducing the risks for cardiovascular events

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DISCLOSURES

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ABSTRACT

BACKGROUND: Standard therapies for the management of stable ischemic heart disease (IHD) partially reduce the risk of a future acute coronary syndrome. Among patients with chronic heart failure or previous myocardial infarction and left ventricular dysfunction, a large body of evidence supports the benefits of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) and, in heart failure, combined therapy with these agents. In contrast, there is less certainty regarding outcomes of ACE inhibitors and ARBs for people with stable IHD who have preserved left ventricular function and no signs or symptoms of heart failure. To compile and synthesize findings derived from research on this specific population, the Agency for Healthcare Research and Quality (AHRQ) commissioned and, in October 2009, published a systematic review and meta-analysis on the benefits and harms of ACE inhibitors and ARBs.

OBJECTIVES: To (a) familiarize health care professionals with AHRQ's 2009 systematic review on ACE inhibitors and ARBs for people with stable IHD and preserved left ventricular function, (b) provide commentary and encourage consideration of the clinical and managed care applications of the review findings, and (c) identify limitations to the existing research on the benefits and harms of ACE inhibitors and ARBs.

SUMMARY: Six trials meeting eligibility criteria provided moderate to strong evidence that, compared with standard therapies alone, ACE inhibitors significantly lower the risks of total mortality, cardiovascular mortality, nonfatal myocardial infarction (MI), stroke, and other clinical outcomes. However, study participants on ACE inhibitors had higher incidences of withdrawals due to adverse events, including syncope, cough, and hyperkalemia. Only 1 trial (TRANSCEND) met eligibility criteria for comparing standard therapies alone versus an ARB (telmisartan). No significant differences were observed for individual clinical endpoints across groups in TRANSCEND, although the composite measure (cardiovascular mortality, nonfatal MI, and stroke) was significantly lower for telmisartan compared with placebo; like ACE inhibitors, ARB therapy increased the risk of hyperkalemia. Only 1 trial (ONTARGET) was identified that compared an ACE inhibitor (ramipril) with an ARB (telmisartan), and this trial showed that ramipril and telmisartan have similar efficacy, similar risks of harms, and therefore a similar balance of benefits to harms. ONTARGET showed that the risk reduction for all clinical endpoints was similar across the 3 treatment arms (ramipril, telmisartan, and combination therapy with ramipril and telmisartan). Combination therapy in ONTARGET was associated with a greater number of total study discontinuations, including discontinuations due to hypotension and syncope. Telmisartan compared with ramipiril had lower rates of cough and angioedema and a higher rate of hypotensive symptoms; there was no difference between ramipril and telmisartan in the rate of syncope. This summary of the AHRQ review also describes the benefits and harms of ACE inhibitors and ARBs in patients who recently had, or were scheduled to have, a revascularization procedure and in different patient subpopulations.

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Stable ischemic heart disease (IHD) is characterized by advanced atherosclerosis, encompassing both large-vessel disease and diffuse microvascular disease. Patients may or may not have had a previous acute coronary syndrome, and the effects of the disease range from asymptomatic ischemic episodes to severe debilitation. Of an estimated 17.6 million adults in the United States who have coronary heart disease (CHD), which is synonymous with IHD, more than 10 million are affected by angina, a common symptom of stable IHD.[1] Regardless of history and symptoms, stable IHD is associated with increased risks of future acute coronary syndrome and premature mortality.[2-4] Standard medical therapy for IHD includes antiplatelet agents (aspirin or clopidogrel), beta-blockers, and, in cases of hypercholesterolemia, statins. Standard medications for relieving the symptoms of stable IHD include fast-acting nitrates, negative chronotropic agents (e.g., beta-blockers or nondihydropyridine calcium channel blockers), and vasodilators (e.g., calcium channel blockers or long-acting nitrates).

Despite the benefits of standard therapies for stable IHD, many patients still experience negative outcomes and remain at relatively high risk of future cardiovascular events.[5,6] Additional treatments that warrant consideration include angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs). Through numerous mechanisms, ACE inhibitors and ARBs may attenuate the influences of angiotensin II on pathogenic cardiovascular remodeling and underlying atherogenic processes, including free radical production, inflammatory mediator release, lymphocyte recruitment, and macrophage accumulation and conversion to foam cells.[7,8] In addition to blocking the conversion of angiotensin I to angiotensin II, ACE inhibitors preserve bradykinin and maintain its vasodilatory effects on the peripheral vasculature. ARBs offer the unique advantage of reducing the effects of angiotensin II regardless of whether it is produced by ACE or non-ACE pathways.

Considerable evidence has demonstrated that therapies directed at angiotensin antagonism or reduction in the effects of angiotensin reduce risks of morbidity and mortality among patients with chronic heart failure and those with a previous MI and left ventricular dysfunction.[9-16] According to the guidelines of the American College of Cardiology and American Heart Association (ACC/AHA), ACE inhibitors are recommended for patients with chronic heart failure, or those with

MI, and left ventricular dysfunction; in this population, ARBs are generally recommended for patients who cannot tolerate ACE inhibitors.[17-19] Although data from 2 trials have suggested the benefit of combined ACE inhibitor and ARB therapy for patients with heart failure, this has not been a consistent observation. The combined use of an ACE inhibitor and ARB in post-myocardial-infarction patients with left ventricular dysfunction or heart failure was no better than the use of captopril alone and carried an increased risk of harm.[13-15] The 2007 ACC/AHA guidelines for managing stable angina state that it is "reasonable" to prescribe ACE inhibitors for patients with preserved left ventricular ejection fraction, well-controlled cardiovascular risk factors, and previous revascularization.[17] Nonetheless, until recently, a systematic review of the effectiveness of ACE inhibitors and ARBs in this population was not available. To address this gap, the Agency for Healthcare Research and Quality (AHRQ) commissioned a systematic review and meta-analysis on the benefits and harms of ACE inhibitors and ARBs in patients with stable IHD and preserved left ventricular systolic function. The review was conducted by researchers at the University of Connecticut/Hartford Hospital Evidence-based Practice Center (EPC). The project was directed by C. Michael White, PharmD, who is a coauthor of this article. In addition to focusing on a patient population that has not been studied extensively, the AHRQ systematic review is unique because it includes analyses of data from the most recent trials on ACE inhibitors and it addresses the comparative effectiveness of combination therapy with ARBs. A full technical report on the systematic review methods and findings, which was published in October 2009, is available on AHRQ's Effective Health Care Program website.[20]

Here we summarize the methods and key findings from the AHRQ review. Consistent with the review's original objectives, this summary is intended to provide evidence to guide clinicians, health care payers, and policy makers in reaching decisions about appropriate therapeutic regimens for patients with stable IHD, preserved left ventricular function, and no history of heart failure. In addition, we seek to encourage readers to reflect on the potential clinical and managed care applications of the systematic review findings.

Key Questions

Consistent with AHRQ's documented procedures for conducting comparative effectiveness research,[21] the topic of ACE inhibitors and ARBs for stable IHD was nominated through an open process. A draft of key questions to guide the systematic review was developed by the AHRQ Scientific Resource Center (SRC) with assistance from clinical specialists and technical experts, including pharmacists, cardiologists, and a managed care representative. The questions were posted on a public website, soliciting input from interested parties. After reviewing the public feedback, the SRC refined a final set of key questions, which were approved by AHRQ. The original questions, relating specifically to people with stable IHD or IHD-risk equivalents and preserved left ventricular systolic function, are summarized as follows.

1. What are the benefits and harms of adding an ACE inhibitor or an ARB to standard therapy compared with standard therapy alone?
2. Among patients who are receiving standard therapy, what are the benefits and harms of combining an ACE inhibitor and an ARB versus using an ACE inhibitor or an ARB alone?
3. Among patients who have recently undergone, or will soon undergo, a coronary revascularization procedure, what are the benefits and harms of adding an ACE inhibitor or an ARB to standard therapy when compared with standard therapy alone?
4. Do the benefits and harms of ACE inhibitors, ARBs, or their combination differ in prespecified subpopulations, such as patients categorized by sex, age, ethnicity, left ventricular ejection fraction, clinical course, and comorbidities?

Systematic Review Methods

This section summarizes the methods by which the EPC researchers conducted their systematic review of published studies on angiotensin-directed therapies. Complete details about the methods are provided in the full technical report.[20]

Literature Search and Study Selection

To identify and obtain study publications, the EPC researchers used comprehensive databases, including MEDLINE®, EMBASE, and the Cochrane Central Register of Controlled Trials. The searches covered periods from database inception through February 2009. In addition, study reports were obtained through manual searches of publications issued by major cardiology organizations. Using prespecified criteria, 2 independent reviewers assessed published studies for inclusion. Studies were selected for full text review if they met the following criteria:

1. Included patients with stable IHD, or a risk equivalent (diabetes mellitus or chronic kidney disease, or mixed vascular atherosclerotic disorders such as coronary disease, peripheral artery disease, or carotid atherosclerosis)
2. Included patients with preserved left ventricular function, defined by an average ejection fraction of greater than 40%, or when left ventricular ejection fraction was not evaluated, exclusion of patients with signs or symptoms of heart failure
3. Compared an ACE inhibitor or an ARB with placebo or active control, or compared combined ACE inhibitor and ARB therapy with either an ACE inhibitor alone or

TABLE 1 Summary of Randomized Controlled Trials Included in the AHRQ Systematic Review (Addressing Key Questions 1, 2, and 4)

Study (Year Published)	Follow-Up Duration	Groups	No. Patients	Mean Age in Years	Male Patients (%)
HOPE (2000)[24]	4.5 years	-Ramipril 10 mg per day -Placebo	9,297	66	72-74
PART-2 (2000)[25]	4.7 years	-Ramipril 5-10 mg per day -Placebo	617	60.5	82
SCAT (2000)[26]	4 years	-Enalapril 20 mg per day -Placebo	460	61	89
EUROPA (2003)[27]	4.2 years	-Perindopril 8 mg per day -Placebo	12,218	60	85-86
CAMELOT (2004)[29]	2 years	-Enalapril 20 mg per day -Amlodipine 10 mg per day -Placebo	1,991	57.7	72-76
PEACE (2004)[31]	4.8 years	-Trandolapril 4 mg per day -Placebo	8,290	64	81-83
SMILE-ISCHEMIA (2007)[32]	6 months	-Zofenopril 60 mg per day	349	58	81-85
TRANSCEND (2008)[33]	4.7 years	-Telmisartan 80 mg per day -Placebo	5,926	67	57
ONTARGET (2008)[37]	56 months	-Ramipril 10 mg per day -Telmisartan 80 mg per day -Ramipril 10 mg per day plus telmisartan 80 mg per day	25,620	66.3	73-74

Source: Baker WL, et al. Ann Intern Med. 2009;151(12):861-71.[52]

CAMELOT = Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis; EUROPA = European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE = Heart Outcomes Prevention Evaluation; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; PART-2 = Prevention of Atherosclerosis with Ramipril Trial 2; PEACE = Prevention of Events with Angiotensin Converting Enzyme Inhibition; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial; SMILE-ISCHEMIA = Survival of Myocardial Infarction Long-term Evaluation-ISCHEMIA; TRANSCEND = Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease.

an ARB alone

4. Included at least 75 patients for controlled clinical trials or at least 1,000 patients for observational studies
5. Followed patients for at least 6 months
6. Reported on at least 1 prespecified efficacy outcome or harm

From a search yielding 1,331 unique citations, 55 citations met the EPC researchers' inclusion criteria without having an exclusion criterion. Given the multiple publications from the large clinical trials discovered in this search, 9 unique randomized controlled trials (RCTs, see Table 1 for summary information) and 3 open label studies were represented. Six systematic reviews also met the eligibility criteria.

Outcomes of Interest and Evaluations of Study Quality and Strength of Evidence

Most of the analyses in the AHRQ review evaluated the efficacy and risks of ACE inhibitors and/or ARBs compared with placebo and, when available, active controls. The main endpoints for clinical outcomes and harms on which these analyses were based are presented in Table 2.

Two independent reviewers assessed the methodological quality of included studies based on their adequacy of randomization, double blinding, and use of intention-to-treat methods.

TABLE 2 Main Outcomes Evaluated in the AHRQ Systematic Review

Benefits	Harms
Total mortality	Withdrawal from trial due to adverse events
Cardiovascular mortality	Hypotension
Nonfatal MI	Syncope
Stroke	Cough
Composite endpoint: cardiovascular mortality, nonfatal MI, stroke	Angioedema
Atrial fibrillation	Hyperkalemia
Symptom reporting	Rash
Hospitalization rates: total, for angina, and for heart failure	Blood dyscrasias
Need for revascularization	
Quality of life measures	

Source: Coleman CI, et al. AHRQ comparative effectiveness report number 18: http://www.effectivehealthcare.ahrq.gov/ehc/products/57/335/ischemic_finalRR1.pdf.[20]

AHRQ = Agency for Healthcare Research and Quality; MI = myocardial infarction.

The strength of evidence derived from the included studies was evaluated using the guidelines of the GRADE Working Group.[22] Evaluations were based on 4 GRADE domains: risk of bias, consistency, directness, and precision. The strength of

evidence for each analysis was graded as *high, moderate,* or *low,* reflecting the extent to which the reviewers were confident that the evidence reflected the true effects of the study interventions.

Statistical heterogeneity was assessed using the Q-statistic and the I^2 index, the latter of which assesses the degree of inconsistency across studies. I^2 values range from 0%-100%, with higher percentages representing a greater likelihood of heterogeneity.[22] I^2 values of 25%-49%, 50%-74%, and greater than 75% are generally interpreted to reflect low, medium, and high statistical heterogeneity, respectively.[23]

Findings for Key Question 1: Comparing ACE Inhibitors or ARBs Added to Standard Therapy Versus Standard Therapy Alone

Twelve studies (N = 41,672 participants), including double-blind RCTs and open-label designs, met the inclusion criteria for comparing the benefits and harms of ACE inhibitors or ARBs added to standard therapy versus standard therapy alone (or an active comparator) in patients with stable IHD[24-33] or IHD risk equivalents[34,35] and preserved left ventricular function. The duration of patient follow-up was 6 months in 1 study[32] and 19.4 months to 4.8 years in the other 11 studies. Nine studies evaluated various ACE inhibitors,[24-27,29-32,34] 2 studies evaluated candesartan,[28,35] and 1 study evaluated telmisartan.[33] Among patients in 4 of the studies, left ventricular ejection fraction ranged from 53%-66%;[28,31,32,35] the remaining 8 studies excluded patients with ejection fractions less than 40% or with signs or symptoms of heart failure. The number of patients using baseline standard therapies varied considerably across the studies (e.g., beta-blockers: 10%-79%; calcium channel blockers: 5%-49%; nitrates: 10%-67%; antiplatelet agents: 53%-93%; statins: 28%-84%; and digoxin: 4%). The use of baseline therapies was most consistent in the 3 largest RCTs: HOPE,[24] EUROPA,[27] and PEACE.[31]

An overview of the main findings to address key question 1 is included in Table 3. The following sections present data from pooled analyses of the comparative benefits and harms of added ACE inhibitors or ARBs versus standard therapy alone.

Key Question 1: Comparative Benefits

Addressing key question 1, the AHRQ review included 2 predesignated sets of analyses that yielded no significant differences in clinical outcomes between study groups. First, in comparisons of an ACE inhibitor versus placebo, incidences of all clinical events did not differ significantly among patients who had stable IHD risk equivalents. Second, in analyses of studies that compared ACE inhibitors with calcium channel blockers, there were no significant differences in clinical outcomes across treatment groups. However, these 2 sets of analyses were based on very few trials, thus compromising the strength of the evidence.

TABLE 3 General Summary of Outcomes and Strength of Evidence Addressing Key Questions 1 and 2

	Key Question 1: ACE Inhibitors Versus Placebo[a,b]	Key Question 1: ARBs Versus Placebo	Key Question 2: Combined Therapy Versus ACE Inhibitor
Total mortality	↓↓↓	– –	– –
Cardiovascular mortality	↓↓	– –	– –
MI[c]	↓↓↓	NE	– –
Stroke	↓↓	– –	– –
Composite of cardiovascular mortality, nonfatal MI, and stroke	– –	↓↓	– –
Study withdrawal due to adverse events	↑	NE	↑↑
Hypotension	–	NE	↑↑
Syncope	↑	NE	↑↑
Cough	↑	NE	– –

[a]*Symbol legend: – (dash) = no significant difference in risk across treatment groups; ↓ = lower risk in patients treated with ACE inhibitor (versus placebo), ARB (versus placebo), or combined therapy (versus ACE inhibitor); ↑ = higher risk in patients treated with ACE inhibitor (versus placebo), ARB (versus placebo), or combined therapy (versus ACE inhibitor).*

[b]*Low strength of evidence indicated by 1 symbol (e.g., ↓); moderate strength of evidence indicated by 2 symbols (e.g., ↓↓); high strength of evidence indicated by 3 symbols (e.g., ↓↓↓).*

[c]*For ACE inhibitors versus placebo and ARB versus placebo (key question 1), this outcome was based on nonfatal MI only; for combined therapy versus ACE inhibitor (key question 2), this outcome included fatal and nonfatal MI.*

Source: Coleman CI, et al. AHRQ comparative effectiveness report number 18, Table 15: http://www.effectivehealthcare.ahrq.gov/ehc/products/57/335/ischemic_finalRR1.pdf.[20]

ACE = angiotensin-converting enzyme; AHRQ = Agency for Healthcare Research and Quality; ARB = angiotensin receptor blocker; MI = myocardial infarction; NE = not evaluated (due to lack of evidence).

Regarding clinical outcomes associated with ARBs, the EPC researchers identified only 1 trial, TRANSCEND, that included patients with stable IHD and preserved left ventricular function.[33] In this trial, 5,926 patients were randomized to receive telmisartan 80 mg per day or placebo; the median duration of follow-up was 56 months. Whereas the major ACE inhibitor trials included a run-in period to ensure that subjects tolerated the therapy, subjects in TRANSCEND were initially not tolerant of ACE inhibitors. All of the following findings for comparison of an ARB versus placebo are based on the results of the TRANSCEND trial.

Mortality outcomes. For the outcome of total mortality, the EPC researchers identified 6 placebo-controlled RCTs that compared ACE inhibitors (ramipril, enalapril, perindopril, or trandolapril) versus placebo.[24-27,29,31] A pooled analysis of the trial results indicated that, over periods of 2.0 to 4.8 years, the risk of total mortality was significantly lower in the ACE

inhibitor arms than the placebo arms (relative risk [RR] = 0.87; 95% confidence interval [CI] = 0.81-0.94; I^2 = 0%). For cardiovascular mortality, a similar finding was observed in the pooled analysis of 5 randomized trials on patients receiving ACE inhibitors or placebo (RR = 0.83; 95% CI = 0.70-0.98; I^2 = 45.5%).[24,25,27,29,31] In contrast, the TRANSCEND trial revealed no significant differences in total mortality (RR = 1.05; 95% CI = 0.91-1.20) or cardiovascular mortality (RR = 1.02; 95% CI = 0.86-1.22) between participants receiving the ARB telmisartan versus placebo.[33]

Nonfatal MI and stroke. The EPC researchers identified 6 RCTs that evaluated nonfatal MI [24-27,29,31] and 7 RCTs that evaluated stroke,[24-27,29-31] among patients receiving ACE inhibitors or placebo. Risks of both outcomes were significantly lower in the ACE inhibitor arms: nonfatal MI (RR = 0.83; 95% CI = 0.73-0.94; I^2 = 30.5%) and stroke (RR = 0.78; 95% CI = 0.63-0.97; I^2 = 37.7%). The applicability of the stroke result is limited because stroke was not consistently defined in the original studies; some trials defined events generally as *stroke*, whereas others reported transient ischemic attacks or broadly defined cerebrovascular accidents. In the TRANSCEND trial, stroke risk was not significantly lower in patients treated with telmisartan versus placebo (RR = 0.83; 95% CI = 0.65-1.06).[33]

Composite outcome. For the composite outcome of cardiovascular mortality, nonfatal MI, and stroke, 2 RCTs were identified that compared an ACE inhibitor (ramipril or trandolapril) to placebo.[24,31] The pooled results of these trials approached but did not achieve statistical significance (RR = 0.85; 95% CI = 0.72-1.01). A similar result was observed in the TRANSCEND trial where, compared with placebo, telmisartan was associated with a significant 12% decrease in the risk of the composite outcome (RR = 0.88; 95% CI = 0.77-1.00).[33] Composite endpoints can sometimes be misinterpreted as yielding reductions similarly across individual endpoints. Please see the individual endpoints above to determine their impact on the composite outcome.

Atrial fibrillation. Placebo-controlled RCTs of ramipril[24] and telmisartan[33] indicated no effect of these therapies on the risk of atrial fibrillation.

Hospitalizations. Separate analyses were performed to evaluate the effects of ACE inhibitors or ARBs on the incidence of total hospitalizations, hospitalization for angina, and hospitalization for heart failure. The only statistically significant effect was observed in a pooled analysis of 5 RCTs that revealed a lower incidence of hospitalizations for heart failure among patients who received an ACE inhibitor versus placebo (RR = 0.78; 95% CI = 0.67-0.90).[24,25,27,29,31]

Need for revascularization. For the comparison of ACE inhibitors versus placebo, 4 RCTs were identified that evaluated the need for revascularization procedures.[24,26,27,29] A pooled analysis indicated that the risk of this outcome was 10% lower in the therapy arms (RR = 0.90; 95% CI = 0.84-0.96). In the single placebo-controlled RCT with an ARB, the relative risk of revascularization was lower among patients treated with telmisartan; however, the analysis did not reach statistical significance (RR = 0.90; 95% CI = 0.79-1.03).[33]

Angina symptoms. One trial that met the review inclusion criteria (the randomized, double-blind, placebo-controlled SMILE-ISCHEMIA study) evaluated anginal symptoms during exercise.[32] In patients performing a treadmill test 6 months after they had an MI, exercise time to onset of ischemic symptoms (mean ± standard deviation) was significantly longer in the ACE inhibitor (zofenopril) arm (6.9 ± 3.1 minutes) compared with the placebo arm (4.4 ± 2.8 minutes; P = 0.024).

Quality of life. No studies that met the AHRQ review inclusion criteria evaluated quality of life outcomes in patients treated with ACE inhibitors or ARBs.

Key Question 1: Comparative Harms

The AHRQ systematic review analyzed risks of harms associated with adding ACE inhibitors or ARBs to standard therapy for stable IHD or IHD risk equivalents in patients with preserved left ventricular function. The main findings from these analyses are summarized as follows (all comparisons are relative to placebo):

- In a pooled analysis of 3 RCTs, ACE inhibitors (ramipril, enalapril, trandolapril) were associated with an increased incidence of study withdrawals due to all adverse events combined (RR = 2.30; 95% CI = 1.34-3.95; I^2 = 87.2%).[25,29,31]
- In a pooled analysis of 2 RCTs with evaluable data, ACE inhibitors (ramipril, trandolapril) were associated with an increased incidence of syncope (RR = 1.24; 95% CI = 1.02-1.52).[24,31]
- In a pooled analysis of 3 RCTs, ACE inhibitors (ramipril, enalapril, trandolapril) were associated with an increased incidence of cough (RR = 1.67; 95% CI = 1.22-2.29; I^2 = 60.2%).[24,29,31]
- Greater incidences of hyperkalemia were observed among patients treated with an ACE inhibitor (ramipril; RR = 1.34; 95% CI = 1.16-1.55)[36] or an ARB (telmisartan; RR = 2.28; 95% CI = 1.63-3.18).[33]

The percentages of study participants who experienced adverse events in association with ACE inhibitors are presented in Table 4. More than half of the studies on which the AHRQ systematic review was based included run-in periods. A relatively large number of patients (up to 17%) were excluded following run-in periods for various adverse events, including some of those evaluated in the AHRQ review. Thus, the true incidence of harms associated with ACE inhibitors outside of clinical trials may be higher than indicated in the review findings.

TABLE 4 Rates of Adverse Events Associated with ACE Inhibitors

Outcomes	Group	Events/Total N (%)	Range in Rates Across Studies (%)	Relative Risk (95% CI)
Withdrawals Due to Adverse Events				
	ACE inhibitors	732/5,139 (14.2)	10.1-15.2	2.30 (1.34-3.95)
	Placebo	343/5,096 (6.7)	1.0-10.8	
Hypotension				
	ACE inhibitors	38/5,490 (0.7)	0.04-9.5	1.79 (0.68-4.71)
	Placebo	26/5,484 (0.5)	0.06-3.2	
Syncope				
	ACE inhibitors	203/8,803 (2.3)	0.06-4.8	1.24 (1.02-1.52)
	Placebo	162/8,784 (1.8)	0.02-3.9	
Cough				
	ACE inhibitors	1,726/9,476 (18.2)	0.3-39.1	1.67 (1.22-2.29)
	Placebo	1,183/9,439 (12.5)	0.2-27.5	

Source: Coleman CI, et al. AHRQ comparative effectiveness report number 18: http://www.effectivehealthcare.ahrq.gov/ehc/products/57/335/ischemic_finalRR1.pdf.[20]

ACE = angiotensin-converting enzyme; AHRQ = Agency for Healthcare Research and Quality.

Only ONTARGET included comparison of the harms associated with an ACE inhibitor versus an ARB. Compared with ramipril, telmisartan had a higher rate of discontinuation of therapy due to hypotension and lower rates of discontinuation due to cough and angioedema; there was no difference between ramipril and telmisartan in discontinuation attributable to syncope, renal impairment, or diarrhea (Table 5).

Findings for Key Question 2: Comparative Benefits and Harms of Combined ACE Inhibitor and ARB Therapy Versus an ACE Inhibitor Alone

Only 1 trial, ONTARGET, met the systematic review inclusion criteria for evaluating the benefits and harms of combining an ACE inhibitor and an ARB versus using 1 of the therapies alone in patients with cardiovascular disease or diabetes mellitus but with no history of chronic heart failure.[37] ONTARGET was a multinational, double-blinded, active-controlled trial. After a run-in period, which ended with 11-18 days of combined therapy (ramipril 5 mg plus telmisartan 40 mg), 25,620 patients were randomly assigned to 1 of 3 groups: (a) ramipril 5 mg per day initially, increased to 10 mg daily after 2 weeks; (b) telmisartan 80 mg daily; or (c) a combination of the 2 agents. Over a 56-month follow-up period, both telmisartan and the combination therapy were evaluated versus ramipril as the active comparator. Over the duration of the study period, the majority of participants reported using standard therapies for cardiovascular disease, including antiplatelets (77%-81%), statins (62%-71%), and beta-blockers (57%).[37]

The primary endpoint of ONTARGET was the composite index of death from cardiovascular causes, MI, stroke, and hospitalization for heart failure. This outcome occurred in 16.3% and 16.5% of patients in the combination therapy and ramipril groups, respectively (RR = 0.99; 95% CI = 0.92-1.07). For all clinical benefits designated by the AHRQ systematic review, ONTARGET revealed no significant differences between combination therapy versus ramipril alone (Table 6). Clinical

Clinical Commentary 1: Assessing the Clinical Significance of Outcomes Associated with ACE Inhibitors

The most consistent findings and strongest evidence derived from the AHRQ systematic review indicate that ACE inhibitors, when added to standard therapies, afford statistically significant benefits to patients with stable IHD and preserved left ventricular function. Compared with placebo, ACE inhibitors were associated with relative risk reductions that ranged from 13%-22% for key clinical outcomes. This magnitude of risk reduction is similar to that observed in trials on the efficacy of ACE inhibitors for patients with a history of MI and left ventricular dysfunction. In a meta-analysis conducted by Dagenais et al. (2006), the results of 3 ACE inhibitor trials in IHD patients with preserved left ventricular function (HOPE, EUROPA, and PEACE; N = 29,805) were pooled and qualitatively compared with the pooled results for 5 ACE inhibitor trials in IHD patients with left ventricular dysfunction (SAVE, AIRE, TRACE, SOLVD-P, and SOLVD-T; N = 12,763).[48] Based on odds ratios (OR), the relative risk reductions associated with ACE inhibitor therapy versus placebo in this meta-analysis were approximately similar between patients with preserved left ventricular function (total mortality OR = 0.86, 95% CI = 0.74-0.94; nonfatal MI OR = 0.82, 95% CI = 0.75-0.91) and patients with left ventricular dysfunction (total mortality OR = 0.80, 95% CI = 0.74-0.87; nonfatal MI OR = 0.77, 95% CI = 0.67-0.88). However, only 9% of control patients with preserved left ventricular function died versus 27% of control patients with left ventricular dysfunction. Thus, the number of patients needed to treat in order to prevent 1 additional event with an ACE inhibitor is qualitatively different across these populations. Based on analyses of trials included in the AHRQ review, to prevent 1 death and 1 nonfatal MI in patients with preserved left ventricular function, the number needed to treat is 91 for both outcomes. In contrast, the meta-analysis reported by Dagenais et al. (2006) indicates that to prevent 1 event in patients with left ventricular dysfunction, the number needed to treat is 26 for total mortality and 56 for nonfatal MI.[48]

TABLE 5 Drug Therapy Discontinuation Due to Harms in ONTARGET

Variable	Ramipril (n = 8,576)	Combination Therapy (n = 8,502)	Telmisartan (n = 8,542)	Combination Versus Ramipril	Telmisartan Versus Ramipril
	n (%)			*P* Values	
Total number of discontinuations	2,099 (24.5)	2,495 (29.3)	1,962 (23.0)	< 0.001	0.02
Hypotension	149 (1.7)	406 (4.8)	229 (2.7)	< 0.001	< 0.001
Syncope	15 (0.2)	29 (0.3)	19 (0.2)	0.03	0.49
Cough	360 (4.2)	392 (4.6)	93 (1.1)	0.19	< 0.001
Angioedema	25 (0.3)	18 (0.2)	10 (0.1)	0.30	0.01
Renal impairment	60 (0.7)	94 (1.1)	68 (0.8)	< 0.001	0.46
Rash	NR	NR	NR	NR	NR
Blood dyscrasias	NR	NR	NR	NR	NR
Diarrhea	12 (0.1)	39 (0.5)	19 (0.2)	< 0.001	0.20

Source: Coleman CI, et al. AHRQ comparative effectiveness report number 18, Table 14: http://www.effectivehealthcare.ahrq.gov/ehc/products/57/335/ischemic_finalRR1.pdf.[20]

NR = not reported; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial.

outcomes were similar despite a greater lowering of blood pressure in the combination therapy group versus the ramipril group. At baseline, mean blood pressure was 142/82 mm Hg for both groups; the mean difference in blood pressure reduction was 2.4/1.4 mm Hg (*P* value was not reported).[37]

Regarding the comparative harms of combination therapy versus ramipril alone, results from the run-period of ONTARGET are noteworthy. Before randomization, potential study participants (N = 29,019) underwent a 21-28 day run-in period in which they started on ramipril 2.5 mg daily and progressed to ramipril 5 mg plus telmisartan 40 mg daily. Of these individuals, 11.7% were not included in the study due to (a) exclusion consequent to poor compliance (3.9%) and unspecified reasons (3.0%); and (b) withdrawal due to symptomatic hypotension (1.7%), elevated serum potassium concentrations (0.8%), elevated serum creatinine concentrations (0.2%), and unspecified reasons (2.1%). Because progression to ramipril plus telmisartan began after the first 3 days of the run-in period, these results may be more attributable to combination therapy than to ramipril alone. It is, of course, uncertain whether exclusions due to poor compliance and unspecified reasons were associated with treatment harms.[37]

The discontinuation rate in ONTARGET was significantly higher in the combination therapy group (29.3%) versus the ramipril group (24.5%, $P < 0.001$). As summarized in Table 6, significantly more discontinuations occurred in the combination therapy group due to hypotension, syncope, and renal impairment. The incidence of cough and angioedema did not differ across the 2 groups. No evidence was available to assess the outcomes of rash or blood dyscrasias.

Clinical Commentary 2: The Payer Perspective on Evaluating Add-On Therapy to Standard Medical Therapy in Managing Stable Ischemic Heart Disease

AHRQ's systematic review addressed the addition of ACE inhibitors and ARBs, alone or in combination, versus standard therapies for stable IHD. The evidence supports adding an ACE inhibitor to standard therapy, with the recognition that patients may discontinue use due to adverse effects. In the event of discontinuation due to cough, an ARB can replace an ACE inhibitor. However, if hyperkalemia is the concern with the ACE inhibitor, switching to an ARB may not be warranted because potassium levels need to be monitored for patients on either ACE inhibitor or ARB therapy. The combination of both agents was not supported and should be reserved by exception only through physician authorization. The evidence for short-term use around revascularization procedures for stable IHD subjects was not strong enough to warrant special considerations beyond those around maintenance therapy for the larger group.

As estimated by the American Heart Association, the direct and indirect costs of cardiovascular disease exceeded $500 billion in 2010.[1] Given that approximately 18 million American adults are affected by coronary heart disease, the treatment investment in managing this important patient population is of significant interest to health plans in general and specifically to those managing the elderly through contracts with the Centers for Medicare & Medicaid Services for Medicare Part D.

In conclusion, the data provided from this AHRQ review support formulary guidance to ensure the cost-effective treatment of this patient group through a stepwise approach of ACE inhibitor and then ARB therapy where warranted, avoiding the unnecessary early use of ARBs. An observational study of such patients following these recommendations would be warranted to provide further evidence of optimizing outcomes and costs for stable IHD patients with preserved left ventricular function.

– Diana Brixner, PhD, RPh

TABLE 6 Comparisons of Combined ACE Inhibitor and ARB Therapy Versus ACE Inhibitor Therapy Alone: Selected Results from ONTARGET

Endpoint	Incidence of Events - n (%)				Relative Risk (95% CI) or *P* Value	
	Ramipril (n = 8,576)		Combination of Telmisartan and Ramipril (n = 8,502)			
Clinical Outcomes						
Total mortality	1,014	(11.8)	1,065	(12.5)	1.07	(0.98-1.16)
Cardiovascular mortality	603	(7.0)	620	(7.9)	1.04	(0.93-1.17)
MI (fatal/nonfatal)	413	(4.8)	438	(5.2)	1.08	(0.94-1.23)
Stroke	405	(4.7)	373	(4.4)	1.08	(0.94-1.23)
Composite endpoint[a]	1,210	(14.1)	1,200	(14.1)	1.00	(0.93-1.09)
Worsening or new angina	567	(6.6)	538	(6.3)	0.96	(0.85-1.08)
Hospitalization for heart failure	354	(4.1)	332	(3.9)	0.95	(0.82-1.10)
Need for revascularization	1,269	(14.8)	1,303	(15.3)	1.04	(0.97-1.13)
Harms						
Total number of discontinuations	2,099	(24.5)	2,495	(29.3)	< 0.001	
Hypotension	149	(1.7)	406	(4.8)	< 0.001	
Syncope	15	(0.2)	29	(0.3)	0.03	
Cough	360	(4.2)	392	(4.6)	0.19	
Angioedema	25	(0.3)	18	(0.2)	0.30	
Renal impairment	60	(0.7)	94	(1.1)	< 0.001	

[a]*Analysis based on the composite outcome defined in the AHRQ systematic review: cardiovascular mortality, myocardial infarction (nonfatal and fatal), or stroke.*

Sources: Yusuf S, et al. N Engl J Med. 2008;358(15):1547-59;37 and Coleman CI, et al. AHRQ comparative effectiveness report number 18: http://www.effectivehealthcare.ahrq.gov/ehc/products/57/335/ischemic_finalRR1.pdf.[20]

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MI = myocardial infarction; ONTARGET = Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial.

Findings for Key Question 3: Benefits and Harms of Angiotensin-Directed Therapies in Proximity to a Coronary Revascularization Procedure

The EPC team identified 7 small (n = 91) to moderate (n = 2,553) size studies in which patients on standard therapies for stable IHD initiated treatment with ACE inhibitors or ARBs before or after undergoing percutaneous coronary intervention (coronary angioplasty with or without stenting or arthrectomy) or coronary artery bypass graft surgery.[38-44] One trial initiated therapy 7-10 days before the procedure, 1 initiated therapy at the same time, and the rest initiated therapy within 7 days after revascularization. Across the 7 studies, the majority of participants were males (76%-91%) who had mean left ventricular ejection fractions above 40%; in 6 of the studies, mean ejection fraction was approximately 60%.

Five studies reported on the need for subsequent revascularization during follow-up periods; among a total of 5,950 patients, the rate for this outcome was 14.1%.[38,41-44] In a pooled analysis of 3 trials comparing ACE inhibitors (cilazapril, quinapril) with placebo, the incidence of need for subsequent revascularizations was significantly greater in patients who initiated the experimental therapy close to their original procedure (RR = 1.29; 95% CI = 1.03-1.60).[38,42,44] In a placebo-controlled trial of candesartan, the need for subsequent revascularizations did not differ significantly across groups (RR = 1.13; 95% CI = 0.32-4.01).[43]

Compared with patients in the placebo group, those who initiated ACE inhibitor or ARB therapy in close proximity to a revascularization procedure were not at significantly greater or less risk for total mortality, cardiovascular mortality, nonfatal MI, stroke, the composite of the previous 3 outcomes, atrial fibrillation, or hospitalizations for angina or heart failure. However, the incidence rates for these outcomes were generally low. Moreover, the studies were relatively short, with follow-up periods ranging from 6 months (in 4 of 6 placebo-controlled trials) to 2.8 years. The trials were not designed to determine how long after a revascularization procedure patients might benefit from initiating ACE inhibitor or ARB therapy.

Scant evidence was available to evaluate harm associated with initiating angiotensin-directed therapies in close proximity to a revascularization procedure. For this key question, the only studies reporting harm involved ACE inhibitors. In 3 placebo-controlled trials, treatment with ramipril or quinapril was associated with a significantly increased risk of withdrawals due to adverse events (RR = 2.18; 95% CI = 1.75-2.71).[39,41,44] In a single trial reporting on hypotension, the risk of this outcome was greater in the ACE inhibitor (quinapril) arm versus the placebo arm (RR = 2.19; 95% CI = 1.67-2.87).[44] In 3 trials, no differences across treatment and placebo groups were observed for cough.[40,42,44] No trials addressing this key question reported the incidence of angioedema, syncope, renal impairment, hyperkalemia, rash, or blood dyscrasias.

Considering the analyses for efficacy and harm, the EPC researchers concluded that the initiation of ACE inhibitor or ARB therapy in close proximity to a revascularization procedure is not favorable for patients with stable IHD and preserved left ventricular function. This does not refer to continuation of ACE inhibitor or ARB therapy in a patient on chronic therapy with these agents.

Findings for Key Question 4: Benefits and Harms of Angiotensin-Directed Therapies by Subpopulation

The AHRQ systematic review evaluated the outcomes from ACE inhibitors, ARBs, or combined therapy among patients categorized by demographic groups (sex, age, ethnicity, left ventricular ejection fraction); clinical course (previous treatment with a stent or coronary artery bypass surgery, degree and location of lesion, presence and pattern of symptoms); dose; comorbidities (diabetes, renal dysfunction, hypertension); and use of other therapies (vitamins, lipid-lowering drugs, beta-blockers, antiplatelet agents). The EPC researchers found few trials that evaluated the comparative benefits and harms of angiotensin-directed therapies in these subpopulations of patients with stable IHD and preserved left ventricular function. Due to insufficient evidence, comparative efficacy outcomes could not be evaluated for the following subpopulation analyses: ethnicity/genetic polymorphisms, left ventricular ejection fraction, degree and location of lesion, presence and pattern of symptoms, and therapy dose. In addition, evidence from the trials included in the review was not sufficient to evaluate harm by subgroups. Thus, to address key question 4, the following summary of findings focuses on efficacy outcomes for which evidence was available.

In subpopulation analyses comparing (a) ACE inhibitors or ARBs with placebo and (b) combination therapy versus an ACE inhibitor, clinical outcomes were not significantly different between males and females, young and older adults, people with versus without diabetes, and people grouped by different levels of hypertension.

Several trials included in the systematic review analyzed clinical outcomes of ACE inhibitors versus placebo in patients with or without renal dysfunction.[45-47] Although the results across trials were not consistent, some evidence suggested that ACE inhibitors reduce the risk of total mortality to a greater extent in patients with renal insufficiency, defined as glomerular filtration rate below 60 mg per mL per 1.73m^2.[45]

Clinical Commentary 3: Informed and Shared Decision Making About Medications for Patients with Stable Ischemic Heart Disease

"Why do I have to be on all these medications?" This is perhaps the most common question that patients ask pharmacists in medication therapy management (MTM) settings. Often, it is the most difficult question to answer in a clear and meaningful way. Patient knowledge regarding each portion of a medication regimen can provide strong support for continued adherence, particularly if the knowledge gained through MTM services is consistent with the patient's health goals and values.

For pharmacists serving patients with stable IHD and preserved left ventricular function, this article provides useful evidence regarding both risks and benefits of ACE inhibitors and ARBs. Patients who are not in close proximity to a revascularization procedure can be educated by the pharmacist and/or physician that initiating an ACE inhibitor will reduce risks of premature death due to any cause or to cardiovascular causes. In addition, pharmacists can use the findings from this review to inform patients that an ACE inhibitor added to their current regimen can reduce the risk of heart attack or stroke.

Use of ARBs as first-line agents in this population is not supported by the available evidence. Pharmacists who interview patients taking an ARB for this indication should seek out a history of intolerance to ACE inhibitors. If there is no such history, the pharmacist and/or physician should counsel the patient on advantages of switching to a generic ACE inhibitor (e.g., more evidence to support efficacy and safety, at lower cost). For patients who have not tolerated ACE inhibitors, the AHRQ review suggests that an ARB may be an appropriate second-line therapy, based on evidence of a reduced risk of the composite outcome of cardiovascular mortality, nonfatal MI, and stroke.

Whereas many patients on ACE inhibitors are familiar with the associated risk of cough, they often know less about the risks of syncope and hyperkalemia. With a strong understanding of the benefits of ACE inhibitors, patients who develop cough may choose to continue their therapy, live with the cough, and save the money that would have been spent switching to an ARB. However, generic losartan and generic losartan-hydrochlorothiazide have been available since April 2010, and the emergence of additional generic ARBs will increase the number of low-cost ARBs. For patients who develop hyperkalemia on an ACE inhibitor, a switch to an ARB may result in a similar outcome; the need for careful monitoring of serum potassium should be discussed with patients to ensure follow-up with lab recommendations.

Finally, as summarized in the AHRQ review, the ONTARGET trial provides evidence for pharmacists to counsel patients about combination therapy with an ACE inhibitor and an ARB. For patients with stable IHD and preserved left ventricular function, ONTARGET indicated a lack of benefit and significant risk of harms (e.g., renal impairment and hypotension) associated with combination therapy. Pharmacists who encounter patients on combination therapy should thus establish the indication and discuss the main findings from the ONTARGET trial with the prescriber.

– Karen Gunning, PharmD, BCPS, FCCP

Five trials analyzed clinical outcomes of ACE inhibitors or ARBs versus placebo in patients grouped by different levels of baseline risk.[24,27,31,33,37] In 1 of these trials, a consistent relationship was observed between higher baseline risk and greater benefits of ACE inhibitor therapy (ramipril).[24]

In a pooled analysis of 2 trials,[24,27] which was originally performed by Dagenais et al. (2006) among patients treated with ACE inhibitors (ramipril or perindopril), the composite risk of cardiovascular death, nonfatal MI, and stroke was significantly lower in those who did not concomitantly use antiplatelet therapy (odds ratio [OR] = 0.60; 95% CI = 0.49-0.73) than in those who used antiplatelet therapy (OR = 0.83; 95% CI = 0.76-0.90; *P* value for interaction < 0.003).[48] Since ACE inhibitors elicit some of their hemodynamic effects through the release of vasodilatory prostaglandins, the concomitant use of nonsteroidal anti-inflammatory drugs such as aspirin may attenuate their benefits.[49,50] A trend toward a better composite outcome was observed for patients without a history of revascularization (OR = 0.74; 95% CI = 0.66-0.82) than in those who had a revascularization procedure (OR = 0.85; 95% CI = 0.75-0.96; *P* value for interaction = 0.078).[48]

Among patients treated with ACE inhibitors, the composite risk of cardiovascular death, nonfatal MI, and stroke was reduced to a similar extent regardless of concomitant use of beta-blockers, lipid-lowering agents, or vitamin E.

Limitations to the Systematic Review Findings

Many of the findings derived from the AHRQ systematic review were based on multicenter and multinational trials with large numbers of participants and long-term follow-up periods. Various issues remain unresolved, however, due to limitations in study samples, designs, and procedures. For example, the reported use of standard treatments for stable IHD varied considerably across trials included in the AHRQ review. Thus, one might question the extent to which ACE inhibitors or ARBs influenced outcomes independently of standard treatments and how the outcomes may have been affected if standard therapy was more consistent. Recognizing this potential limitation, the review authors contend that it is reasonable to attribute their findings to the effects of the therapies studied, especially ACE inhibitors, because they observed relatively low to moderate levels of statistical heterogeneity and there was general agreement in effect sizes across studies.

The AHRQ review findings also raise the question of whether clinical outcomes observed in patients treated with ACE inhibitors, ARBs, or combined therapy are attributable mainly to the blood-pressure-lowering effects of these agents. As observed in the CAMELOT trial, for example, the ACE inhibitor enalapril and the calcium channel blocker amlodipine were associated with similar reductions in blood pressure, which corresponded to similar benefits in clinical outcomes.[29] However, several other trials—including HOPE, EUROPA, and TRANSCEND—demonstrated that clinical outcomes were not explained by treatment-associated reductions in blood pressure among patients with stable IHD and preserved left ventricular function.[24,27,33] In other words, the effects of ACE inhibitors and ARBs on the clinical outcomes evaluated in the AHRQ review appear largely attributable to mechanisms that were independent of changes in blood pressure.

The largest trials on which the review was based (HOPE, EUROPA, PEACE, and TRANSCEND) included patients whose mean age ranged from 60 to 67 years.[24,27,31,33] Whereas the incidence of coronary heart disease is relatively low among people below age 60, risk factors such as diabetes mellitus and hypertension are now fairly common in younger adults. Thus, given the restricted age range of patients in the trials included in the AHRQ review, generalization of the findings across age groups may be problematic. Because the majority of study participants were males, applications to females are also limited.

Only 1 trial (TRANSCEND) that met the review's inclusion criteria compared the benefits and harms of adding an ARB to standard therapy versus using standard therapy alone. Because this trial was limited to participants who could not tolerate ACE inhibitors, its results apply to a select patient subpopulation. Moreover, due to insufficient evidence, firm conclusions could not be reached for comparisons of ACE inhibitors or ARBs versus calcium channel blockers and for outcomes of ACE inhibitor or ARB therapy in patients with IHD risk equivalents.

As summarized in this article, the AHRQ systematic review is based on evidence from study reports published up until February 2009. However, no new clinical trial evidence has been reported in the intervening period that would alter the review conclusions. Despite controversy regarding the impact of ARBs on the development of cancer, a recent meta-analysis did not find an increased risk.[51]

Conclusions and Key Areas for Future Research

As summarized in Table 3, for the population of people with stable IHD and preserved left ventricular function, the main findings from the AHRQ systematic review indicate that the addition of an ACE inhibitor to standard medical therapy is associated with clinical benefits but increased risks of syncope and cough. For individual clinical endpoints, no advantages are gained by adding an ARB to standard medical therapy or by combining an ACE inhibitor and an ARB. Moreover, combination therapy poses increased risks of harms. To address knowledge gaps identified through conducting the review, its authors call for future comparative effectiveness studies and meta-analyses to evaluate benefits and harms in minority groups, including Asians, African-Americans, and Latinos; patients with single-vessel versus multi-vessel disease; patients with varying levels of baseline left ventricular function; and patients taking PGY12 inhibitors drugs versus no antiplatelet therapy to

determine whether the observed interaction between antiplatelet therapies and ACE inhibitors is applicable to all antiplatelets agents or to aspirin only (and the doses of these medications). The authors also recommend more extensive future trials to compare the effectiveness and safety of adding ACE inhibitors or ARBs to standard medical therapy versus adding agents such as calcium channel blockers and vasoactive drugs such as thiazide diuretics. Among other important subpopulation analyses that have yet to be performed, the authors recommend future trials to determine whether angiotensin-directed therapy outcomes differ among patients with polymorphisms within the ACE gene or the angiotensin II type 1 receptor.

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Supplement